

AMENDED SPECIFICATION

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PATENT SPECIFICATION

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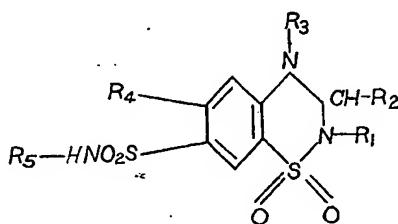
COMPLETE SPECIFICATION

3:4-Dihydro-1:2:4-Benzothiadiazine-1:1-Dioxides

We, CIBA LIMITED, a body corporate organised according to the laws of Switzerland, of Basle, Switzerland, do hereby declare the invention, for which we pray that a patent

5 may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

10 The present invention relates to the manufacture of 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxides of the general formula

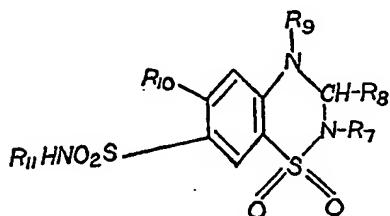


15 and salts of these compounds especially with alkali metals in which R₁, R₃ and R₅ stand for hydrogen or alkyl radicals, especially with 1 to 5 carbon atoms, R₂ for hydrogen, an aliphatic hydrocarbon radical having 1 to 8 carbon atoms, a cycloalkyl, a cycloalkenyl, a 20 cyclolalkyl-alkyl, a cycloalkenyl-alkyl, a phenyl, a phenyl alkyl, a heterocyclyl or heterocyclalkyl radical, the heterocyclic radical of these latter being monocyclic and containing one oxygen, nitrogen or sulphur atom in the ring, [Pri]

all these radicals being either unsubstituted or substituted by halogen atoms, free, esterified or etherified hydroxyl or mercapto groups, nitro, acylamino, mono alkyl-, dialkyl or N,N-alkylene-amino groups, whose alkylene radical has 4 to 5 carbon atoms and may be interrupted by a hetero-atom, carboxyl groups or alkyl groups containing 1 to 5 carbon atoms, R₄ for an unsubstituted or halogen substituted alkyl radical having 1 to 5 carbon atoms, an alkoxy group having 1 to 5 carbon atoms or a halogen atom and, when R₂, R₃ and R₅ represent hydrogen and R₄ represents chlorine, R₁ stands for an alkyl radical. As aliphatic hydrocarbon radicals there may be mentioned more especially alkyl radicals, such as methyl, ethyl, propyl, isopropyl, butyl or pentyl radicals, or alkenyl radicals, such as vinyl or 1-propenyl radicals or alkynyl radicals, for example the ethynyl radical. The cycloaliphatic radicals, such as cycloalkyl or cycloalkenyl radicals, are for example cyclopentyl or cyclohexenyl, or cyclohexyl-ethyl or cyclohexenyl-ethyl radicals. As phenylalkyl radicals there may be mentioned for example benzyl or 2-phenyl-ethyl radicals and as heterocyclic and heterocyclic-alkyl radicals primarily furyl, thieryl, pyridyl, furfuryl or thieryl-methyl radicals.

25 30 35 40 45 50 55 The new 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxides show diuretic and natriuretic effects and are intended for use as medicaments.

Particularly pronounced diuretic activity is shown by the compounds of the formula



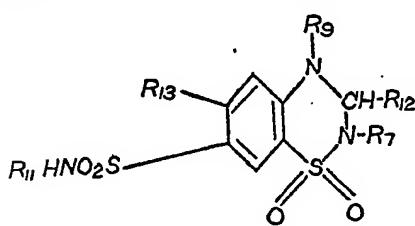
or their salts in which formula R_n, R₉ and R₁₁ stand for hydrogen or an alkyl radical having 1—5 carbon atoms, R₈ for hydrogen, an unsubstituted aliphatic hydrocarbon radical with 1—8 carbon atoms or an aliphatic hydrocarbon radical with 1—8 carbon atoms and substituted by halogen, free, esterified or etherified hydroxyl or amino groups, a cyclo-

5 substituted aliphatic hydrocarbon radical with 1—8 carbon atoms or an aliphatic hydrocarbon radical with 1—8 carbon atoms and substituted by halogen, free, esterified or etherified hydroxyl or amino groups, a cyclo-

10 alkyl, a cycloalkenyl, a phenyl, a pyridyl, a thienyl, a phenyl, a furyl or a furfuryl radical or a phenyl alkyl radical, R₁₀ for halogen, alkoxy with 1—5 carbon atoms, unsubstituted or halogen-substituted alkyl having 1—5

15 carbon atoms, and in which formula R_n represents an alkyl group having 1—5 carbon atoms when R₉, R₈ and R₁₁ represent hydrogen and R₁₀ chlorine.

Outstanding as regards activity are the compounds of this group of the general formula



and their salts, in which formula R_n, R₉ and R₁₁ have the meanings given above, R₁₂ stands for hydrogen, an unsubstituted alkyl group with 1—5 carbon atoms or an alkyl group with

25 1—5 carbon atoms substituted by amino or hydroxyl groups, or halogen atoms, the cyclohexenyl, benzyl or phenylethyl radical and R₁₃ for halogen, such as bromine, fluorine and especially chlorine, or an alkyl radical with 1—5 carbon atoms, and in which R_n stands for an alkyl radical with 1—5 carbon atoms when R₉, R₁₁ and R₁₂ represent hydrogen and R₁₃ represents chlorine.

35 As compounds having an especially outstanding activity there may be mentioned the 3 - n - propyl- and the 3 - isopropyl - 6 - chloro - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide, the 3 -

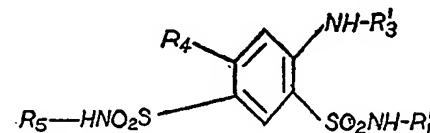
40 3 - n - butyl- and the 3 - isobutyl - 6 - chloro - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide, the 3 - chloromethyl - 6 - chloro - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine -

45 1:1 - dioxide, the 3 - ethoxy- methyl- and the 3 - phenoxyethyl - 6 - chloro - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide, the 3-benzyl-

and the 3 - (2¹ - phenylethyl) - 6 - chloro - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide, the 3 - cyclohex - 3¹ - enyl - 6 - chloro - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide, the 2-methyl- and the 4 - methyl - 6 - chloro - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide and the 2 - methyl - 6 - chloro - 7 - methylsulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide and the salts thereof.

The new compounds may be used as medicaments in the form of pharmaceutical preparations which contain the compounds in admixture or conjunction with a pharmaceutical organic or inorganic, solid or liquid carrier suitable for enteral, e.g. oral, or parenteral administration. For making up the preparations there may be employed substances which do not react with the new compounds, such as water, gelatine, lactose, starches, magnesium stearate, talc, vegetable oils, benzyl alcohols, gums, polyalkylene glycols, petroleum jelly, cholesterol or any other known carrier for medicaments. The pharmaceutical preparations may be in solid form, for example, as tablets, dragees or capsules, or in liquid form as solutions, suspensions or emulsions. If desired, they may be sterilised and/or contain auxiliary substances, such as preserving agents, stabilisers, wetting or emulsifying agents, salts for varying the osmotic pressure or buffers. They may also contain other therapeutically useful substances, for example hypotensive agents, such as Rauwolfia or Veratrum alkaloids, e.g. reserpine, rescinnamine, deserpidine, germine or protoveratrine, synthetic hypotensive agents, e.g. hydralazine, or ganglionic blockers, such as chlorisondamine.

The new compounds are obtained by reacting a 2-sulphamyl-aniline of the formula



in which R₄ and R₅ have the meanings given above and R_{1'} and R_{3'} stand for hydrogen or an alkyl radical, or a salt thereof, with an aldehyde of the formula R₂CHO in which R₂ has the meaning given above, and, if desired, but in any case when R₁, R₂, R₃, R₄ and R₅ stand for hydrogen and R₄ for a chlorine atom, treating the resulting compounds having substitutable nitrogen atoms with an agent capable of introducing an alkyl radical. The reaction with the aldehyde is preferably carried out in the presence of an acid, such as a mineral acid, e.g. a hydrohalic acid, such as hydrochloric acid or hydrobromic acid or sulphuric acid, if

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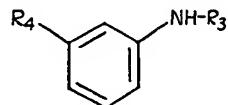
desired, in anhydrous form. The aldehyde of the formula $R_2\text{CHO}$ can also be used in the form of one of its polymers or reactive functional derivatives, e.g. paraformaldehyde, trioxane, hexamethylene-tetramine, or of an acetal, e.g. dimethoxymethane, diethoxymethane, 1:1-dimethoxyethane or 1:1-diethoxyethane. The reaction is carried out primarily with approximately equivalent quantities of the reaction components. With higher quantities of aldehyde the yields may be diminished owing to its reacting with the



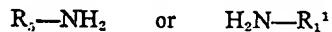
group. The reaction can be carried out in the absence or preferably in the presence of a solvent, such as an ether, e.g. para-dioxane or diethyleneglycol-dimethyl ether, or of a formamide, e.g. dimethylformamide, at room temperature or at an elevated temperature and under atmospheric or superatmospheric pressure or in the presence of an inert gas, such as nitrogen. As a salt of the 2-sulphamyl-aniline there is used in this reaction more especially a salt with an alkali metal or with an acid, primarily with an inorganic acid, such as hydrohalic acid, e.g. hydrochloric acid or hydrobromic acid.

The starting materials used in this reaction are known or can be made by methods in

themselves known. The 2-sulphamyl-anilines are obtained by reacting an aniline of the formula



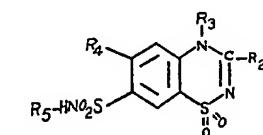
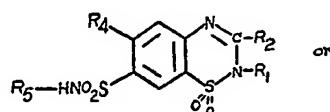
in which R_3 and R_4 have the meanings given above. The reaction may also be carried out, with a halogensulphonic acid, e.g. chloro-sulphonic acid, and subsequently with ammonia, preferably liquid or in aqueous solution, or with an amine of the formula



in which R_1^1 and R_5 have the meanings given above. The reaction may also be carried out in stages, first by introducing a halogenosulphonyl group, then converting the latter into the sulphamyl radical and then introducing the second halogenosulphonyl group and converting the latter into the amide. In this way the starting materials are prepared in which the substituents of the amide group can be different from one another.

Another method for the preparation of the new compounds consists in reducing the $\text{C}=\text{N}$ -double bond in benzothiadiazine - 1:1-dioxides of the general formula

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in which R_1 , R_2 , R_3 , R_4 and R_5 have the meanings given above, and, if desired, but in any case when R_1 , R_2 , R_3 and R_5 stand for hydrogen and R_4 for a chlorine atom, treating the resulting compounds having substitutable nitrogen atoms with an agent capable of introducing an alkyl radical. The reduction is preferably carried out with a di-metal hydride, primarily with an alkali metal boronhydride, such as lithium, potassium or especially sodium boronhydride. These metal hydrides are used in the presence of a solvent, such as an aqueous solution of an alkali metal hydroxide, e.g. lithium, sodium or potassium hydroxide, of an ether, such as diethyleneglycol dimethyl ether, or of a liquid carboxylic acid amide, such as a formamide, e.g. formamide itself or dimethyl formamide. The reduction can be carried out at room temperature or at an elevated temperature, if desired, in the presence of an inert gas, such as nitrogen. The $\text{C}=\text{N}$ -double bond can also be reduced electrolytically by methods known per se.

The starting materials used for the above method are known or can be made by methods known per se.

In resulting sulphamyl - 3:4 - dihydro-1:2:4 - benzothiadiazine - 1:4 - dioxides containing substitutable nitrogen atoms the hydrogen atoms of the nitrogen groupings can be replaced by alkyl radicals by methods known per se. Thus, alkyl radicals, such as methyl or ethyl radicals, can be introduced by reacting a solution of the resulting sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxides in aqueous alkali metal hydroxide, such as lithium, sodium or potassium hydroxide solution, with a reactive ester of an alcohol, such as a dialkyl sulphate, e.g. dimethyl or diethyl sulphate. Mono- or poly-substituted products may be formed.

Depending on the conditions of the reaction the new compounds are obtained in free form or in the form of a salt thereof. A resulting metal salt can be converted into the free compound for example by reaction with an aqueous acid agent, such as a mineral acid, e.g. hydrohalic acid, for example hydrochloric acid or sulphuric acid. A free compound can be converted into a metal salt, such as an alkali metal salt by treatment e.g. with a metal hydroxide, such as sodium or potassium hydroxide, in a solvent, such as an alkanol, e.g.

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methanol or ethanol, or in water and evaporating the solvent; or by reacting the free compound in an ether, such as para-dioxane or diethyleneglycol dimethyl ether solution, with 5 an alkali metal hydride or amide, e.g. sodium or potassium hydride or amide. Mono- or polysalts may be obtained.

Any resulting racemate may be converted 10 into the antipodes thereof according to the methods for resolving racemates.

The invention also relates to any modification of the process in which those starting materials are used and worked up that the 15 compounds described as being especially valuable are obtained.

The invention also comprises any modification of the process in which a compound obtainable as an intermediate at any stage of the process is used as starting material and the 20 remaining steps are carried out, or in which a starting material is formed under the reaction conditions.

The following Examples illustrate the invention:

EXAMPLE 1

A mixture of 2.9 g. of 5 - chloro - 2:4 - disulphamyl - aniline in 20 ml. of anhydrous diethyleneglycol dimethylether, 0.44 g. of acetaldehyde and 0.5 ml. of a solution of hydrogen chloride in ethyl acetate (109.5 g. hydrogen chloride per 1000 ml.) is heated to 80—90° C. and maintained at that temperature for 1 hour. The reaction mixture is concentrated under reduced pressure; on addition of water, 30 the product separates and is then recrystallized from ethanol or aqueous ethanol to yield the desired 6 - chloro - 3 - methyl - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide, m.p. 258—260° C.

The same product is obtained by replacing the acetaldehyde by 0.9 g. of 1:1-dimethoxyethane or by 1.2 g. of 1:1-diethoxy-ethane.

EXAMPLE 2

The 6 - chloro - 3 - ethyl - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide and 6 - chloro - 3 - ethoxy-methyl - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide 50 may be prepared by substituting in Example 1, an equivalent amount of propionaldehyde or 2-ethoxyacetaldehyde, respectively for the acetaldehyde of the reference example and otherwise following the procedure recited therein.

EXAMPLE 3

A mixture of 3.4 g. of 5 - bromo - 2:4 - disulphamylaniline in 15 ml. of anhydrous diethyleneglycol dimethylether, 0.33 g. of paraformaldehyde and 0.5 ml. of a saturated solution of hydrogen chloride gas in ethyl acetate is heated to 80—90° C. for one hour. After cooling, the solution is concentrated under reduced pressure to one third of its 60 volume diluted with water, then allowed to

crystallize. The product is filtered off and recrystallized from water to yield the desired 6 - bromo - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide.

EXAMPLE 4

A solution of 1.0 g. of 2:4 - disulphamyl - 5 - fluoro - aniline, m.p. 233—236° C., in 5 ml. of diethyleneglycol dimethylether is treated with 0.1 g. of paraformaldehyde and 0.2 ml. of a saturated solution of hydrogen chloride gas in ethyl acetate, and the reaction mixture is heated to 80—90° C. for one hour. After cooling, the solution is concentrated under reduced pressure, water is added, and the aqueous solution is further concentrated. The crystalline material is filtered off and recrystallized from water to give the 6 - fluoro - 7 - sulphamyl - 3:4 - dihydro - benzothiadiazine - 1:1 - dioxide, m.p. 229—231° C.

EXAMPLE 5

To a solution of 5.8 g. of 5 - chloro - 2,4 - disulphamyl - aniline in 30 ml. of diethyleneglycol dimethylether are added 2.2 g. of benzaldehyde and 1 ml. of a saturated solution of hydrogen chloride in ethyl acetate, and the reaction mixture is kept at 80—90° C. for one hour. After cooling, concentrating under reduced pressure and diluting with water an oil separates which crystallizes upon trituration with ether. The resulting 6 - chloro - 3 - phenyl - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide is recrystallized from aqueous ethanol, m.p. 246—249° C.

By using 4 - chloro - benzaldehyde or 3:4: 5 - trimethoxy - benzaldehyde in lieu of benzaldehyde, the 3 - (4¹ - chlorophenyl) - 6 - chloro - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide and the 3 - (3¹:4¹:5¹ - trimethoxyphenyl) - 6 - chloro - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide, respectively, may be prepared.

EXAMPLE 6

By reacting 2.9 g. of 5 - chloro - 2:4 - disulphamyl - aniline in 15 ml. of diethyleneglycol dimethylether with 0.75 g. of isobutyraldehyde in the presence of 0.5 ml. of a saturated solution of hydrogen chloride in ethyl acetate at 80—90° C. the crystalline 6 - chloro - 3 - isopropyl - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide precipitates after about ten minutes. It is recrystallized from dimethylformamide by adding hot water to the solution, m.p. 304—306° C.

EXAMPLE 7

By reacting 0.75 g. of *n*-butyraldehyde with 2.9 g. of 5 - chloro - 2:4 - disulphamyl-aniline according to the process of Example 6, the 6 - chloro - 3 - *n* - propyl - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide can be obtained after heating to 80—90° C. for one hour, concentrating under reduced pressure and diluting

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with water. It is recrystallized from aqueous ethanol and melts at 254-256° C.

EXAMPLE 8

5 A mixture of 2.9 g. of 5 - chloro - 2:4-
disulphamyl - aniline, 1.2 g. of 2 - thiophene-
carboxaldehyde and 0.5 ml. of a saturated
10 solution of hydrogen chloride in ethyl acetate
in 15 ml. of diethyleneglycol dimethylether is
reacted at 80-90° C. for one hour and then
concentrated under reduced pressure. On
15 addition of water an oil separates which
crystallizes slowly. The 6 - chloro - 7 -
sulphamyl - 3 - (2 - thiienyl) - 3:4 - dihydro-
1:2:4 - benzothiadiazine - 1:1 - dioxide is
20 recrystallized from ethanol, m.p. 222-225° C.

By using the 2 - thiophene - acetaldehyde instead of the thiophene - carboxaldehyde, the 3 - (2 - phenyl) - 6 - chloro - 7 - sulphamyl-
25 3:4 - dihydro - 1:2:4 - benzothiadiazine-
1:1 - dioxide can be prepared according to
the above-given procedure.

EXAMPLE 9

25 A solution of 4.62 g. of 5 - methoxy - 2:4-
disulphamyl - aniline in 70 ml. of diethyleneglycol dimethylether is treated with 0.4 g. of
30 paraformaldehyde and 1.0 ml. of a saturated
solution of hydrogen chloride in ethyl acetate
at 80-90° C. for two hours. The 6 -
methoxy - 7 - sulphamyl - 3:4 - dihydro-
35 1:2:4 - benzothiadiazine - 1:1 - dioxide
precipitates after concentrating under reduced
pressure and diluting with water and is
recrystallized from aqueous ethanol, m.p. 254-
257° C.

EXAMPLE 10

To a solution of 5.8 g. of 5 - chloro - 2:4-
40 disulphamyl - aniline in 30 ml. of diethyleneglycol dimethylether are added 2.2 g. of
pyridine-4-aldehyde and 1.0 ml. of a saturated
solution of hydrogen chloride in ethyl acetate.
The mixture is allowed to stand at room
45 temperature for one hour and is then heated
to 80-95° C. for one additional hour. After
concentrating under reduced pressure, the residue
is diluted with water, the supernatant solution
50 decanted and ethanol added to the oily precipitate. The 6 - chloro - 3 - (4-pyridyl) - 7 - sulphamyl - 3:4 - dihydro-
1:2:4 - benzothiadiazine - 1:1 - dioxide
crystallizes slowly and melts above 310° C.

EXAMPLE 11

55 A solution of 5.4 g. of 2:4 - disulphamyl -
5 - methyl - aniline in 40 ml. of diethyleneglycol dimethylether is treated with 0.6 g. of
paraformaldehyde and 1.5 ml. of a concentrated
solution of hydrogen chloride in ethyl acetate and held at 80-100° C. for one hour.
A crystalline material precipitates after
60 concentrating under reduced pressure and adding
water. The 6 - methyl - 7 - sulphamyl - 3:4 -
dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide
is filtered off and recrystallized from
65 a 1:1-mixture of dimethylformamide and
water, m.p. 263-265° C.

EXAMPLE 12

A mixture of 2.5 g. of 5 - chloro - 2:4-
disulphamyl-aniline, 1.0 g. of 2-furaldehyde,
0.5 ml. of a concentrated solution of hydro-
gen chloride in ethyl acetate and 15 ml. of
70 diethyleneglycol dimethylether is heated to 80-
90° C. for one hour, then concentrated
under reduced pressure. Water is added to
precipitate an oil which crystallizes upon
75 trituration with aqueous ethanol. After recrystallization
from aqueous ethanol the 6 - chloro-
3 - (2¹ - furyl) - 7 - sulphamyl - 3:4 - dihydro-
1:2:4 - benzothiadiazine - 1:1 - dioxide
melts at 214-218° C. z

EXAMPLE 13

To a solution of 2.9 g. of 5 - chloro - 2:4-
disulphamyl-aniline in 15 ml. of diethyleneglycol dimethylether are added 0.9 g. of iso-
80 valeraldehyde and 0.5 ml. of a saturated solution
of hydrogen chloride in ethyl acetate. The
reaction mixture is heated for one hour to 80-
90° C., then concentrated under reduced
pressure. An oily material precipitates on the
85 addition of water, the water is decanted and
ethanol added. The 6 - chloro - 3 - isobutyl-
7 - sulphamyl - 3:4 - dihydro - 1:2:4-
benzothiadiazine - 1:1 - dioxide crystallizes,
is filtered off and recrystallized from a mixture
90 of dimethylformamide and water, m.p.
241-245° C. 95

EXAMPLE 14

A mixture of 2.9 g. of 5 - chloro - 2:4-
disulphamyl - aniline, 1.53 g. of chloroacetyl-
aldehyde diethylacetal and 0.5 ml. of a saturated
100 solution of hydrogen chloride in ethyl acetate in 15 ml. of diethyleneglycol dimethylether
is heated to 80-90° C. for one hour and then concentrated under reduced pressure.
Water and ether are added to the residue
105 which crystallizes slowly. The 6 - chloro-
3 - chloro - methyl - 7 - sulphamyl - 3:4 -
dihydro - 1:2:4 - benzothiadiazine - 1:1 -
dioxide is recrystallized from aqueous ethanol,
m.p. 235° C. (with decomposition).

EXAMPLE 15

To a solution of 2.9 g. of 5 - chloro - 2:4-
disulphamyl - aniline in 15 ml. of diethyleneglycol dimethylether are added 1.2 g. of
phenylacetaldehyde and 0.5 ml. of a saturated
110 solution of hydrogen chloride in anhydrous
ethyl acetate. The reaction mixture is heated to
90-100° C. for two hours and then concentrated
under reduced pressure. Water is added; a syrupy material precipitates, whereupon the water is
115 decanted and on addition of ethanol to the residue, the 3 - benzyl - 6 -
chloro - 7 - sulphamyl - 3:4 - dihydro - 1:
2:4 - benzothiadiazine - 1:1 - dioxide precipitates. It is recrystallized from a mixture
of dimethylformamide and water, m.p. 247-
250° C. 125

By using 4 - chloro - phenylacetaldehyde,
3:4:5 - trimethoxyphenylacetaldehyde or 3-
methyl - phenylacetaldehyde instead of phenyl-
120 acetaldehyde in the above procedure the 3-
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5 (4¹ - chlorobenzyl) - 6 - chloro - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide, 3 - (3¹:4¹:5¹ - trimethoxybenzyl) - 6 - chloro - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide or 3 - (3¹ - methyl - benzyl) - 6 - chloro - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide, respectively, may be obtained.

10 EXAMPLE 16

10 A mixture of 2.9 g. of 5 - chloro - 2:4 - disulphamyl - aniline, 15 ml. of diethyleneglycol dimethylether, 1.1 g. of *n*-valeraldehyde and 0.5 ml. of a saturated solution of hydrogen chloride in anhydrous ethyl acetate is heated to 80-90° C. for two hours. The reaction mixture is concentrated under reduced pressure, water is added to the residue and then decanted from the oily precipitate. Upon 15 addition of ethanol and standing at room temperature some unreacted 5 - chloro - 2:4 - disulphamyl - aniline separates; the filtrate is then evaporated to dryness. The residue is treated with benzene and then with aqueous 20 ethanol to yield the 3 - *n* - butyl 6 - chloro - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide, which after recrystallization from aqueous ethanol melts at 176-179° C.

30 EXAMPLE 17

30 A mixture of 1.0 g. of 5 - chloro - 2:4 - disulphamyl - N - methyl - aniline, 10 ml. of diethyleneglycol dimethylether, 0.09 g. of paraformaldehyde and 0.25 ml. of a saturated 35 solution of hydrogen chloride in anhydrous ethyl acetate is heated to 80-100° C. for one hour. After cooling, the reaction mixture is concentrated under reduced pressure, water is added to the residue and the resulting crystalline 40 6 - chloro - 4 - methyl - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide is recrystallized from aqueous ethanol, m.p. 225-227° C.

EXAMPLE 18

45 A mixture of 2.0 g. of 5 - chloro - 2:4 - di - (N - methyl - sulphamyl) - aniline, 20 ml. of diethyleneglycol dimethylether, 0.18 g. of paraformaldehyde and 0.5 ml. of a saturated solution of hydrogen chloride in anhydrous ethyl acetate is heated for one hour to 50 about 80-90° C., then cooled, evaporated under reduced pressure and the residue diluted with water. The water is decanted, ethanol and water are added, whereupon a crystalline 55 material is formed, which is filtered off. The 6 - chloro - 2 - methyl - 7 - (N - methylsulphamyl) - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide is dissolved in ethanol and water is added to precipitate the 60 desired product, which is filtered off, m.p. 203-206° C.

65 The starting material used in the above reaction may be prepared as follows: 3.25 g. of 5 - chloro - aniline - 2:4 - disulphonyl chloride is treated with 20 ml. of a 25 per

cent aqueous solution of methylamine at room temperature for 30 minutes and then on the steam bath for an additional 15 minutes. The reaction mixture is cooled, filtered and the isolated 5 - chloro - 2:4 - di - (N - methylsulphamyl) - aniline is twice recrystallized from a 1:1-mixture of ethanol and water, m.p. 186-190° C.

EXAMPLE 19

70 2.6 g. of 6 - chloro - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide is dissolved in 11 ml. of 1N aqueous sodium hydroxide and 40 ml. of water. The solution is cooled to 10° C., 1.4 g. of dimethylsulphate is added and the mixture is stirred at 10° C. for one hour and at room temperature for an additional hour. The solid material is filtered off to yield 2.8 g. of a wet material, which is recrystallized four times 80 from a mixture of ethanol and water, to yield the 6 - chloro - 2 - methyl - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide, m.p. 240-245° C. From the mother liquor, the 6 - chloro - 2 - methyl - 7 - (N - methyl - sulphamyl) - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide, m.p. 203-206° C. can be recovered, which is identical with the product obtained according to the procedure of Example 18.

EXAMPLE 20

90 A mixture of 2.5 g. of 5 - chloro - 2:4 - disulphamyl - aniline, 1.4 g. of 2 - carboxybenzaldehyde, 1 ml. of a saturated solution of hydrogen chloride in ethyl acetate and 50 ml. of diethyleneglycol dimethylether is heated to 90° C., one third of the solvent is stripped off and the rest is poured into water. After standing at room temperature, the water is decanted, the residue is again washed with water and the resulting 3 - (2¹ - carboxyphenyl) - 6 - chloro - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide is recrystallized from a mixture of ethanol and water, m.p. 340-345° C.

95 The following compounds are prepared according to the above procedure by using different aldehydes or acetals with lower alkanols, e.g. methanol or ethanol, thereof:

100 6 - chloro - 3 - (2¹ - fluorophenyl) - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide m.p. 248-250° C.

105 6 - chloro - 3 - (3¹ - fluorophenyl) - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide m.p. 227-229° C.

110 6 - chloro - 3 - (2¹ - methylphenyl) - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide m.p. 263-266° C.

115 6 - chloro - 3 - (3¹ - methylphenyl) - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide m.p. 232-235° C.

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6 - chloro - 3 - (3¹ - hydroxyphenyl) - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide
m.p. 238-240° C. 70

5 6 - chloro - 3 - (4¹ - isopropylphenyl) - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide, (crystallizes probably with ethanol)
m.p. 225° C. 75

10 3 - bromomethyl - 6 - chloro - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide
m.p. 215-216° C. 75

15 6 - chloro - 3 - dichloromethyl - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide
m.p. 242-244° C. 80

EXAMPLE 21 85

A mixture of 5.7 g. of 5 - chloro - 2:4 - disulphamyl - aniline, 3.2 g. of diethylamino-pivalaldehyde and one pellet of sodium hydroxide in 60 ml. of 90% aqueous ethanol is heated on the steam bath for one hour. Two-thirds of the solvent is removed, water is added and the solution is neutralized with dilute aqueous hydrochloric acid. The resulting precipitate is collected and recrystallized by dissolving the 6 - chloro - 3 - (1¹:1 - dimethyl-2¹ - diethylamino - ethyl) - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide in dimethyl-formamide and adding this solution to hot water, m.p. 288-290° C. 90

EXAMPLE 22 95

A mixture of 5.6 g. of 5 - chloro - 2:4 - sulphamyl - aniline, 4.0 g. of 1:1 - diethoxy-2 - piperidino - (N) - ethane and 7 ml. of ethyl acetate saturated with hydrogen chloride in 50 ml. of diethylene glycol dimethylether is heated for one hour on the steam bath. Crystalline material precipitates, which is collected and recrystallized from ethanol to yield the 6 - chloro - 3 - piperidino - (N)-methyl - 7 - sulphamyl - 3:4 - dihydro-1:2:4 - benzothiadiazine - 1:1 - dioxide hydrochloride, m.p. 208-210° C. 100

The hydrochloride is dissolved in water, the solution is made neutral with sodium carbonate, whereupon the 6 - chloro - 3 - piperidino - (N) - methyl - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide precipitates and is filtered off, m.p. 150-152° C. 105

EXAMPLE 23 110

A mixture of 5.7 g. of 5 - chloro - 2:4 - disulphamyl - aniline, 2.2 g. of 3 - cyclohexenyl - carboxaldehyde and 1 ml. of ethyl acetate saturated with hydrogen chloride in 50 ml. of diethylene glycoldimethylether is heated on the steam bath for one hour. Two-thirds of the solvent is stripped off under reduced pressure; the residue is added to water while stirring. The crystalline 6 - chloro - 3 - (3¹ - cyclohexenyl) - 7 - sulphamyl - 3:4 - dihydro-1:2:4 - benzothiadiazine - 1:1 - dioxide is collected and recrystallized from methanol, m.p. 252-254° C. 115

In a manner analogous to that described there may be prepared other compounds containing in the 3-position, for example, a 2-cyclopentyl-ethyl-, a cyclopentyl-, a cyclohexyl-, a cyclohexenyl-methyl-, a cyclohexenyl-ethyl radical. The chlorine atom in 6-position may be replaced, choosing appropriate starting materials, by for example bromine or trifluoromethyl. 120

EXAMPLE 24 125

To a solution of 5.8 g. of 5 - chloro - 2:4 - disulphamyl - aniline in 30 ml. of diethylene glycol dimethylether are added 1 ml. of a 2N solution of hydrogen chloride in anhydrous ethyl acetate and 4.2 g. of phenoxy-acetaldehyde diethylacetal, and the reaction mixture is heated to 80-90° C. for one hour. The solvents are removed under reduced pressure, the residue is triturated with hexane and on addition of water, a crystalline material is formed. The 6 - chloro - 3 - phenoxyethyl - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide is recrystallized from aqueous dimethyl-formamide, m.p. 262-264° C. 130

EXAMPLE 25 130

To a solution of 1.2 g. of 3 - acetoxy-methyl - 6 - chloro - 7 - sulphamyl - 1:2:4 - benzothiadiazine - 1:1 - dioxide in 30 ml. of diethylene glycol dimethylether is added 0.3 g. of sodium borohydride. The reaction mixture is allowed to stand at room temperature for 1½ hours and is then concentrated under reduced pressure. Water is added to the residue and the solution is neutralized with diluted aqueous hydrochloric acid. The solvent is removed under reduced pressure, water is added and the solid material is filtered off; the 3 - acetoxyethyl - 6 - chloro - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide is recrystallized twice from aqueous dimethyl-formamide, m.p. 264-265° C. 130

The starting material is prepared by reacting 5 - chloro - aniline - 2:4 - disulphamyl chloride with acetoxy-glycolic acid chloride, followed by treatment with ammonia to yield the desired 3 - acetoxy - methyl - 6 - chloro-7 - sulphamyl - 1:2:4 - benzothiadiazine - 1:1 - dioxide, m.p. 310-312° C. 130

EXAMPLE 26 130

A mixture of 5.8 g. of 5 - chloro - 2:4 - disulphamyl - aniline, 3.5 g. of acetamido-acetaldehyde diethylacetal (prepared by treatment of amino-acetaldehyde diethylacetal with acetic acid anhydride, b.p. 101-104° C./0.6 mm.) and 1 ml. of a 2N solution of hydrogen chloride in anhydrous ethyl acetate in 30 ml. of diethylene glycol dimethylether is heated on the steam bath for one hour, then cooled and concentrated under reduced pressure. The resulting crystalline material is recrystallized from aqueous ethanol to yield the 3 - acet-

amidomethyl - 6 - chloro - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide, m.p. 258-260° C.

EXAMPLE 27

5 To a solution of 5.8 g. of 5 - chloro - 2:4 - disulphamyl - aniline in 30 ml. of diethylene glycol dimethylether are added 10 ml. of a 2N solution of hydrogen chloride in anhydrous ethyl acetate and 3.7 g. of 1:1 - diethoxy-
10 2 - diethylamino - ethane. The reaction mixture is heated on the steam bath for one hour; two layers are formed and after cooling, the diethylene glycol dimethylether layer is decanted. 30 ml. of water is added to the lower
15 layer and on addition of sodium carbonate and 30 ml. of ether, a crystalline precipitate is formed. The 6 - chloro - 3 - diethylamino-
20 methyl - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide is filtered off and recrystallized three times from aqueous dimethyl-formamide, m.p. 196° C. (decomposition).

By substituting 3.22 g. of 1:1 - diethoxy-
25 2 - dimethylamino - ethane for the 1:1 - diethoxy - 2 - diethylamino - ethane in the above example, the 6 - chloro - 3 - dimethylamino-
30 methyl - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide can be obtained, m.p. 184° C. (decomposition).

EXAMPLE 28

A mixture of 5.8 g. of 5 - chloro - 2:4 - disulphamyl - aniline, 2.9 g. of 1:1 - diethoxy-
35 2 - methylamino - ethane and 10 ml. of a 2N solution of hydrogen chloride in anhydrous ethyl acetate in 30 ml. of diethylene glycol dimethylether is treated as described in Example 28. The crystalline product obtained after neutralization with sodium carbonate is dissolved in ethyl acetate, the solution is concentrated and hexane added. The resulting precipitate crystallizes on addition of ether. The 6 - chloro - 3 - methylamino - methyl - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide is recrystallized from aqueous ethanol, m.p. 163° C. (decomposition).

EXAMPLE 29

1 g. of 3 - propyl - 6 - chloro - 7 - sulphamyl - 1:2:4 - benzothiadiazine - 1:1 - dioxide is dissolved in 20 ml. of N:N-dimethyl-formamide and 30 ml. of 2N-aqueous sulphuric acid is added. This solution is placed into the cathode chamber of an electrolytic cell having a mercury cathode of 20.5 cm² surface. The cathode chamber is separated from the anode chamber by a porous clay membrane ("Alundum" (Registered Trade Mark) membrane). The anolyte consists of a 2:3-mixture of N:N-dimethylformamide and 2N-aqueous sulphuric acid; a platinum electrode is used as the anode. Direct current is applied; at a temperature of from 15 to 20° C., the initial current density is 0.163 amp/cm², which after a reaction time of 24 minutes drops to 0.059 amp/cm². The reference

potential versus a standard calomel electrode is -1.3 V.

The catholyte is neutralized with 35 ml. of 2N aqueous sodium hydroxide, concentrated to a small volume, filtered and the filtrate concentrated to dryness. The residue is triturated with water, the resulting 3 - propyl - 6 - chloro - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide is filtered off and recrystallized from water, m.p. 254-256° C. A mixture of the resulting product and the compound prepared according to the method described in Example 7 does not show any melting point depression.

The sodium salt may be prepared by evaporating the solution of 3 - phenyl - 6 - chloro - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide in an equimolar amount of aqueous sodium hydroxide.

EXAMPLE 30

To a solution of 2.9 g. of 5 - chloro - 2:4 - disulphamyl - aniline in 15 ml. of diethylene-glycol dimethylether are added 1.2 g. of phenylacetaldehyde and 0.5 ml. of a saturated solution of hydrogen chloride in anhydrous ethyl acetate. The reaction mixture is heated to 90-100° C. for two hours and then concentrated under reduced pressure. Water is added; a syrupy material precipitates, whereupon the water is decanted and, on addition of ethanol to the residue, the 3 - benzyl - 6 - chloro - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide precipitates. It is recrystallized from a mixture of dimethylformamide and water, m.p. 247-250° C.

By using 4 - chloro - phenylacetaldehyde, 3:4:5 - trimethoxy - phenylacetaldehyde or 3 - methyl - phenylacetaldehyde instead of phenylacetaldehyde in the above procedure the 3 - (4¹ - chlorobenzyl) - 6 - chloro - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide, 3 - (3¹:4¹:5¹ - trimethoxybenzyl) - 6 - chloro - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide or 3 - (3¹ - methylbenzyl) - 6 - chloro - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide, respectively, may be obtained.

By treating a solution of the resulting 3 - benzyl - 6 - chloro - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide in aqueous sodium hydroxide with dimethylsulphate at 10-20° C. for one hour and at room temperature for an additional hour a mixture of 3 - benzyl - 6 - chloro - 2 - methyl - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:17 - dioxide and 3 - benzyl - 6 - chloro - 2 - methyl - 7 - (N - methyl - sulphamyl) - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide can be obtained which may be separated into the single components by fractionated crystallization.

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EXAMPLE 31

5 A solution of 3 - benzyl - 6 - chloro - 7 - sulphamyl - 1:2:4 - benzothiadiazine - 1:1 - dioxide in diethyleneglycol dimethyl-ether is treated with sodium borohydride and the mixture is allowed to stand at room temperature. The solution is adjusted to pH=7 after filtration, and the resulting precipitate is recrystallized to yield the desired 3 - benzyl - 6 - chloro - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide, which is identical with the product obtained according to the procedure described in Example 31.

10 The starting material may be prepared by allowing to stand a solution of 5 - chloroaniline - 2:4 - disulphonylchloride in phenyl-acetyl chloride for one day at room temperature, collecting the resulting N - phenylacetyl-5 - chloro - aniline - 2:4 - disulphonylchloride and treating it with an excess of liquid ammonia, removing the unreacted ammonia at room temperature and heating the residue to 200° C. for three hours and crystallizing the desired 3 - benzyl - 6 - chloro - 7 - sulphamyl - 1:2:4 - benzothiadiazine - 1:1 - dioxide.

15 By replacing in the preparation of the starting material the 5 - chloro - aniline - 2:4 - disulphonylchloride with 5 - methyl - aniline-2:4 - disulphonylchloride, the 3 - benzyl-6 - methyl - 7 - sulphamyl - 1:2:4 - benzothiadiazine - 1:1 - dioxide is obtained which can be converted to the 3 - benzyl - 6 - methyl-7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide by treatment of an aqueous sodium hydroxide solution with sodium borohydride.

EXAMPLE 32

20 A solution of 5 - chloro - 2:4 - disulphonyl - aniline in 30 ml. of diethyleneglycol dimethyl-ether is treated with 1 ml. of a saturated solution of hydrogen chloride in ethyl acetate and 2.68 g. of 3 - phenyl-propionaldehyde. The reaction mixture is heated to 70-90° C. for one hour, then concentrated under reduced pressure to a small volume, and 30 ml. of water is added. The 6 - chloro - 3 - (2¹ - phenylethyl) - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide crystallizes, is filtered off, recrystallized from ethanol (m.p. 117-119° C.; probably crystallizes with ethanol) and dried at 80° C., m.p. 174-175° C.

25 The following compounds can be prepared by varying in the previously described methods the starting materials and proceeding according to the given procedures: 6 - fluoro - 3 - (2¹ - phenylethyl) - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide, 6 - bromo - 3 - (2¹ - phenylethyl) - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide, 6 - methyl-3 - (2¹ - phenylethyl) - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide, 6 - chloro - 3 - [2¹ - 3¹¹ - methyl-

phenyl] - ethyl] - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide, 6 - chloro - 3 - [2¹ - (4¹¹ - methyl-phenyl) - ethyl] - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide, 6 - chloro - 3 - [2¹ - (4¹¹ - isopropyl-phenyl) - ethyl] - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide, 6 - chloro - 3 - [2¹ - (4¹¹ - methoxy-phenyl) - ethyl] - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide, 6 - chloro - 3 - [2¹ - (3¹¹:4¹¹ - dimethoxy - phenyl) - ethyl] - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide, 6 - chloro - 3 - [2¹ - (4¹¹ - methylenedioxy - phenyl) - ethyl] - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide, 6 - chloro - 3 - [2¹ - (3¹¹:4¹¹ - trimethoxy - phenyl) - ethyl] - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide, 6 - chloro - 3 - [2¹ - (3¹¹:4¹¹ - dimethoxy - phenyl) - ethyl] - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide, 6 - chloro - 3 - [2¹ - (3¹¹:4¹¹ - methylenedioxy - phenyl) - ethyl] - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide, 6 - chloro - 3 - [2¹ - (3¹¹:4¹¹ - nitro - phenyl) - ethyl] - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide, 6 - chloro - 3 - [2¹ - (4¹¹ - nitro - phenyl) - ethyl] - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide, 6 - chloro - 3 - [2¹ - (4¹¹ - chloro-phenyl) - ethyl] - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide, 6 - chloro - 3 - [2¹ - (2¹¹:5¹¹ - dibromo - phenyl) - ethyl] - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide or 6 - chloro - 3 - [-2¹ - (4¹¹ - fluoro - phenyl) - ethyl] - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide.

EXAMPLE 33

30 A mixture of 5.6 g. of 5 - chloro - 2:4 - disulphonyl - aniline, 2.6 g. of 2 - phenyl-propionaldehyde, 1 ml. of a saturated solution hydrogen chloride in ethyl acetate and 25 ml. of diethyleneglycol is heated on the steam bath for one hour, concentrated to about one-half of the original volume, diluted with water and worked up as described in Example 33. The 6 - chloro - 3 - (1¹ - phenylethyl) - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide is obtained in yellow crystals after recrystallization from aqueous ethanol, m.p. 226-228° C.

EXAMPLE 34

35 To a solution of 5.9 g. of 5 - chloro - 2:4 - disulphonyl - aniline in 30 ml. of diethyleneglycol dimethylether are added 1 ml. of a 2N solution of hydrogen chloride in ethyl acetate and 3.2 g. of ethoxy-acetaldehyde diethylacetal and the mixture is heated to 80-90° C. for one hour and then cooled. Upon

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concentration under reduced pressure and addition of water an oily product is formed; the water is decanted and on addition of ether a crystalline material precipitates, which is 5 filtered off. The 6 - chloro - 3 - ethoxy-methyl - 7 - sulphamyl - 3:4 - dihydro-1:2:4 - benzothiadiazine - 1:1 - dioxide is recrystallized three times from a 1:1-mixture of ethanol and water, m.p. 186—190° C.

10 **EXAMPLE 35**
9.4 g. of 6 - chloro - 3 - methyl - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide is dissolved in a mixture of 33 ml. of 1N aqueous sodium hydroxide and 120 ml. of water; undissolved material is filtered off. After cooling to 10° C. dimethyl sulphate (4.2 g.) is added and kept at that temperature for one hour and for an additional hour at room temperature. The 15 reaction mixture is filtered and the crystalline material recrystallized twice from a 1:1-mixture of ethanol and water to yield 6-chloro - 2:3 - dimethyl - 7 - sulphamyl-3:4 - dihydro - 1:2:4 - benzothiadiazine-1:1 - dioxide, m.p. 274—276° C.

20 The recrystallization mother liquors are concentrated, the residue solidifies and is recrystallized from methanol, followed by recrystallization from aqueous ethanol to yield 25 6 - chloro - 2:3 - dimethyl - 7 - (N - methyl-sulphamyl) - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide, m.p. 248—251° C.

30 The starting material may be prepared as follows: A mixture of 2.9 g. of 5 - chloro-2:4 - disulphamyl - aniline, 20 ml. of anhydrous diethyleneglycol dimethyl-ether, 0.44 g. 35 acetaldehyde and 0.5 ml. of a solution of hydrogen chloride in ethyl acetate (109.5 g. hydrogen chloride per 1000 ml.) is heated to 80—90° C. and maintained at that temperature for 1 hour. The reaction mixture is concentrated under reduced pressure; on addition of water, the crystalline product 40 separates and is then recrystallized from ethanol and aqueous ethanol to yield the desired 6 - chloro - 3 - methyl - 7 - sulphamyl-3:4 - dihydro - benzothiadiazine - 1:1 - dioxide, m.p. 258—260° C.

45 **EXAMPLE 36**
To a solution of 12.2 g. of 6 - chloro - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide in a mixture of 55 ml. of 1N aqueous sodium hydroxide and 50 200 ml. of water is added 6.9 ml. of diethyl sulphate. The reaction mixture is stirred at 10—20° C. for about 5½ hours and then allowed to stand at room temperature overnight. A viscous material is separated from the solution, dissolved in a small amount of ethanol; unreacted starting material is filtered off. After standing at room temperature for some time, the crystalline 6 - chloro - 2-ethyl - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide is filtered off 55 and recrystallized from aqueous ethanol, m.p. 195—198° C.

60 **EXAMPLE 37**
A solution of 10.6 g. of 3 - n - butyl - 6 - chloro - 7 - sulphamyl - 3:4 - dihydro-1:2:4 - benzothiadiazine - 1:1 - dioxide in 66 ml. of 1N aqueous sodium hydroxide and 120 ml. of water is cooled to below 20° C. and 65 4.2 g. of dimethyl sulphate is added dropwise. The reaction mixture is stirred at that temperature for one hour, and is extracted with three portions of ethyl acetate. The organic layer is dried over sodium sulphate, the solvent is evaporated to leave an amorphous mixture consisting of 3 - n - butyl - 6 - chloro - 2 - methyl - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide and 3 - n - butyl - 6 - chloro - 2 - methyl - 7 - (N - methyl - sulphamyl) - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide contaminated with unreacted starting material; it melts at 90—95° C. (with decomposition and foaming).

70 **EXAMPLE 38**
A solution of 7 - sulphamyl - 6 - trifluoromethyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide in aqueous sodium hydroxide is treated with dimethyl sulphate at about 10° C.; the resulting crystalline mixture may be separated into the 2 - methyl - 7 - sulphamyl - 6 - trifluoromethyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide and the 2 - methyl - 7 - (N - methyl-sulphamyl) - 6 - trifluoromethyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide by fractionated crystallization.

75 The starting material may be prepared as follows: To a solution of 0.85 g. of 2:4-disulphamyl - 5 - trifluoro - methyl - aniline in 20 ml. of diethyleneglycol dimethyl-ether are added 0.08 g. paraformaldehyde and 0.5 ml. of a saturated solution of hydrogen chloride in ethyl acetate and the reaction mixture is heated to 95° C. for two hours. The volume is brought to one-half by removal of the solvent, water is added, and the crystalline material is recrystallized from aqueous ethanol to yield the desired 7 - sulphamyl - 6 - trifluoromethyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide, m.p. 198—200° C.

80 Other 2-lower alkyl 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxides may be prepared according to the previously-outlined procedure.

85 **EXAMPLE 39**
To a solution of 3.42 g. of 5 - chloro-2:4 - di - (N - ethyl - sulphamyl) - aniline in 25 ml. of diethyleneglycol dimethyl-ether are added 0.3 g. of paraformaldehyde and 0.5 ml. of a saturated solution of hydrogen chloride in ethyl acetate. The mixture is heated to 80—90° C. for one hour, the solvent is removed and water is added to the syrupy residue. The water is decanted, the residue 90

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is dissolved in a small volume of warm ethanol and crystallizes upon cooling to yield the 6-chloro - 2 - ethyl - 7 - (N - ethyl - sulphamyl) - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide; it melts at 163-166° C. after recrystallization from aqueous ethanol.

EXAMPLE 40

By reacting 4.0 g. of 5 - chloro - 2:4 - di-(N - n - butyl - sulphamyl) - aniline in 20 ml. diethylene glycol dimethyl-ether with 0.3 g. paraformaldehyde in the presence of 0.5 ml. of a saturated solution of hydrogen chloride in ethyl acetate according to the procedure described in Example 40 the 2 - n - butyl - 7 - (N - n - butyl - sulphamyl) - 6 - chloro - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide is obtained, m.p. 170-171° C.

EXAMPLE 41

The new 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide compounds of this invention may be made up into pharmaceutical compositions. For example, the 3 - butyl - 6 - chloro - 7 - sulphamyl - 3:4 - dihydro-1:2:4 - benzothiadiazine - 1:1 - dioxide may be formulated into tablets containing 0.05 g. of active material according to the following procedure (for 1000 tablets):

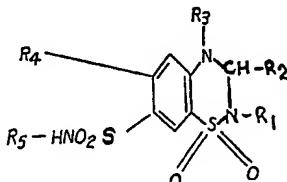
Ingredients:

3-butyl-6-chloro-7-sulphamyl-3:4-dihydro-1:2:4-benzothiadiazine-1:1-dioxide	50.00 g.	30
Lactose Spray dried	124.00 g.	
Polyethylene glycol 6000	8.00 g.	
Tragacanth BC, U.S.P.	4.00 g.	35
Sucrose, U.S.P.	3.00 g.	
Talc, U.S.P.	10.00 g.	
Magnesium Stearate	1.00 g.	
Distilled water and ethanol	q.s.	

The benzothiadiazine-1:1-dioxide, tragacanth, lactose, sucrose, talc and magnesium stearate are screened through a 20 mesh sieve and mixed together for twenty minutes. The polyethylene glycol is dissolved in a mixture of 15 ml. water and 15 ml. of alcohol. The mixed powders are wetted with this solution; the moist mass is passed through a 10 mesh screen and then dried at 38° with circulating air until moisture content is from about two to about three per cent. The granules are broken on a 16 mesh sieve and compressed into tablets of 0.20 g. weight by using 10/32" punches and dies.

WHAT WE CLAIM IS:—

1. 3:4 - Dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxides of the formula



in which R₁ and R₃ each represent a hydrogen atom or an alkyl radical, R₅ represents a hydrogen atom, R₂ represents a hydrogen atom, an aliphatic hydrocarbon radical having 1 to 8 carbon atoms or a phenyl, a phenyl-alkyl, a heterocycl or heterocycl-alkyl radical, the heterocyclic radical of these latter being monocyclic and containing one oxygen, nitrogen or sulphur atom in the ring, all these radicals being either unsubstituted or substituted by halogen atoms or free hydroxyl or alkoxy groups containing 1 to 5 carbon atoms, dialkylamino groups or alkyl groups containing 1 to 5 carbon atoms, R₄ represents a halogen atom or an alkoxy group having 1 to 5 carbon atoms or an unsubstituted alkyl group having 1 to 5 carbon atoms, and, when R₂, R₃ and R₅ represent hydrogen and R₂ represents chlorine, R₁ represents an alkyl radical, and physiologically tolerable salts of these compounds.

2. 3:4 - Dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxides and physiologically

tolerable salts thereof as claimed in claim 1, in which R₁, R₃, R₄ and R₅ have the meanings given in claim 1, and R₂ represents an unsubstituted phenyl or phenyl-alkyl radical or such a radical substituted by halogen, alkyl containing 1 to 5 carbon atoms, alkoxy containing 1 to 5 carbon atoms or dialkylamino groups, or represents an aliphatic hydrocarbon radical having 1 to 8 carbon atoms which is unsubstituted or substituted by alkoxy containing 1 to 5 carbon atoms or dialkylamino groups.

3. 3:4 - Dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxides and physiologically tolerable salts thereof as claimed in claim 1, in which R₁, R₃, R₄ and R₅ have the meanings given in claim 1, and R₂ represents an aliphatic hydrocarbon radical having 1 to 5 carbon atoms substituted by halogen.

4. 3:4 - Dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxides of the formula given in claim 1 and physiologically tolerable salts thereof, in which R₁, R₂, R₃ and R₄ have the

5	meanings given in claim 1, and R_5 represents alkyl, or in which R_5 represents hydrogen or alkyl, R_1 , R_3 and R_4 have the meanings given in claim 1, and R_2 represents an aliphatic hydrocarbon radical having 1 to 8 carbon atoms, a phenyl, a phenyl-alkyl, a heterocycl or heterocycl-alkyl radical, the heterocyclic radical of these latter being monocyclic and containing one oxygen, nitrogen or sulphur atom in the ring, and all these radicals being substituted by free mercapto- or alkyl-mercaptop groups having 1 to 5 carbon atoms.	10	10. 6 - Bromo - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide.
10		11. 6 - Fluoro - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide.	70
15	5. 3:4 - Dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxides of the formula given in claim 1 and physiologically tolerable salts thereof, in which R_1 , R_2 , R_3 and R_5 have the means given in any one of the preceding claims, and R_4 represents a halogen-substituted alkyl having 1 to 5 carbon atoms, with the exception of compounds wherein R_1 , R_3 and R_5 represent H, R_4 stands for the trifluoromethyl group, and R_2 represents H, an alkyl group, an unsubstituted phenyl group or a phenyl-alkyl group, the phenyl radical of which may be substituted with a halogen atom or an alkyl or alkoxy group containing 1 to 5 carbon atoms.	20	12. 3 - Isopropyl - 6 - chloro - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide.
20	6. 3:4 - Dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxides of the formula given in claim 1 and physiologically tolerable salts thereof, in which R_1 , R_3 , R_4 and R_5 have the means given in any one of claims 1, 4 and 5, and R_2 represents a cycloalkyl, a cycloalkenyl, a cycloalkyl-alkyl or a cycloalkenyl-alkyl group, which is unsubstituted or substituted by a halogen atom, a free hydroxyl or mercapto group, an alkoxy- or alkyl-mercaptop group containing 1 to 5 carbon atoms, a dialkylamino group or an alkyl group containing 1 to 5 carbon atoms.	25	13. 3 - (2 - Thienyl) - 6 - chloro - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide.
25	7. 3:4 - Dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxides of the formula given in claim 1, and physiologically tolerable salts thereof, in which R_1 , R_3 , R_4 and R_5 have the meanings given in any one of claims 1, 4 and 5, and R_2 represents an aliphatic hydrocarbon radical having 1 to 8 carbon atoms, a cycloalkyl, a cycloalkenyl, a cycloalkyl-alkyl, a cycloalkenyl-alkyl, a phenyl, a phenyl alkyl, a heterocycl or heterocycl-alkyl radical, the heterocyclic radical of these latter radicals being monocyclic and containing one oxygen, nitrogen or sulphur atom in the ring, and all these radicals being substituted by etherified or esterified hydroxyl or mercapto groups, nitro, acylamino, monoalkylamino or N : N -alkylene-amino groups, whose alkylene radical has 4 to 5 carbon atoms and may be interrupted by a hetero atom, or carboxyl groups.	30	14. 3 - n - Propyl - 6 - chloro - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide.
30	8. 3 - Methyl - 6 - chloro - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide.	35	15. 3 - (2 - Phenyl) - 6 - chloro - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide.
35	9. 3 - Ethyl - 6 - chloro - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide.	40	16. 3 - (4 - Pyridyl) - 6 - chloro - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide.
40	10. 3 - (2 - Furyl) - 6 - chloro - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide.	45	17. 6 - Methoxy - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide.
45	11. 3 - Isobutyl - 6 - chloro - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide.	50	18. 3 - (4 - Chlorophenyl) - 6 - chloro - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide.
50	12. 3 - (2 - Chloromethyl) - 6 - chloro - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide.	55	19. 6 - Methyl - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide.
55	13. 3 - (2 - Benzyl) - 6 - chloro - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide.	60	20. 3 - (2 - Butyl) - 6 - chloro - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide.
60	14. 3 - (2 - (3 - Methyl - phenyl) - 6 - chloro - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide.	65	21. 3 - (2 - (3 - Hydroxy - phenyl) - 6 - chloro - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide.
65	15. 3 - (2 - (3 - (1 - Methyl - phenyl) - 6 - chloro - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide.	70	22. 3 - (2 - (3 - (1 - Hydroxy - phenyl) - 6 - chloro - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide.
70	16. 3 - (2 - (3 - (1 - (2 - Methyl - phenyl) - 6 - chloro - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide.	75	23. 3 - (2 - (3 - (1 - (2 - (2 - Methyl - phenyl) - 6 - chloro - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide.
75	17. 3 - (2 - (3 - (1 - (2 - (2 - (2 - Methyl - phenyl) - 6 - chloro - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide.	80	24. 3 - (2 - (3 - (1 - (2 - (2 - (2 - (2 - Methyl - phenyl) - 6 - chloro - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide.
80	18. 3 - (2 - (3 - (1 - (2 - (2 - (2 - (2 - (2 - Methyl - phenyl) - 6 - chloro - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide.	85	25. 3 - (2 - (3 - (1 - (2 - (2 - (2 - (2 - (2 - Methyl - phenyl) - 6 - chloro - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide.
85	19. 3 - (2 - (3 - (1 - (2 - (2 - (2 - (2 - (2 - (2 - Methyl - phenyl) - 6 - chloro - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide.	90	26. 3 - (2 - (3 - (1 - (2 - (2 - (2 - (2 - (2 - (2 - Methyl - phenyl) - 6 - chloro - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide.
90	20. 3 - (2 - (3 - (1 - (2 - (2 - (2 - (2 - (2 - (2 - Methyl - phenyl) - 6 - chloro - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide.	95	27. 3 - (2 - (3 - (1 - (2 - (2 - (2 - (2 - (2 - (2 - Methyl - phenyl) - 6 - chloro - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide.
95	21. 3 - (2 - (3 - (1 - (2 - (2 - (2 - (2 - (2 - (2 - Methyl - phenyl) - 6 - chloro - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide.	100	28. 3 - (2 - (3 - (1 - (2 - (2 - (2 - (2 - (2 - (2 - Methyl - phenyl) - 6 - chloro - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide.
100	22. 3 - (2 - (3 - (1 - (2 - (2 - (2 - (2 - (2 - (2 - Methyl - phenyl) - 6 - chloro - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide.	105	29. 3 - (2 - (3 - (1 - (2 - (2 - (2 - (2 - (2 - (2 - Methyl - phenyl) - 6 - chloro - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide.
105	23. 3 - (2 - (3 - (1 - (2 - (2 - (2 - (2 - (2 - (2 - Methyl - phenyl) - 6 - chloro - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide.	110	30. 3 - (2 - (3 - (1 - (2 - (2 - (2 - (2 - (2 - (2 - Methyl - phenyl) - 6 - chloro - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide.
110	24. 3 - (2 - (3 - (1 - (2 - (2 - (2 - (2 - (2 - (2 - Methyl - phenyl) - 6 - chloro - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide.	115	31. 3 - (2 - (3 - (1 - (2 - (2 - (2 - (2 - (2 - (2 - Methyl - phenyl) - 6 - chloro - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide.
115	25. 3 - (2 - (3 - (1 - (2 - (2 - (2 - (2 - (2 - (2 - Methyl - phenyl) - 6 - chloro - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide.	120	32. 3 - (2 - (3 - (1 - (2 - (2 - (2 - (2 - (2 - (2 - Methyl - phenyl) - 6 - chloro - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide.
120	26. 3 - (2 - (3 - (1 - (2 - (2 - (2 - (2 - (2 - (2 - Methyl - phenyl) - 6 - chloro - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide.	125	33. 3 - (2 - (3 - (1 - (2 - (2 - (2 - (2 - (2 - (2 - Methyl - phenyl) - 6 - chloro - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide.
125	27. 3 - (2 - (3 - (1 - (2 - (2 - (2 - (2 - (2 - (2 - Methyl - phenyl) - 6 - chloro - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide.	130	34. 3 - (2 - (3 - (1 - (2 - (2 - (2 - (2 - (2 - (2 - Methyl - phenyl) - 6 - chloro - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide.

benzothiadiazine - 1:1 - dioxide.	thiadiazine - 1:1 - dioxide.	50
32. 3 - (4 ¹ - Isopropyl - phenyl) - 6-chloro - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide.	48. 4 - Methyl - 6 - chloro - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide.	
5 33. 3 - (3 ¹ :4 ¹ :5 ¹ - Trimethoxyphenyl)-6 - chloro - 7 sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide.	49. 2 - Methyl - 6 - chloro - 7 - (N-methyl - sulphamyl) - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide and salts thereof.	55
10 34. 3 - Bromomethyl - 6 - chloro - 7-sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide.	50. 2 - Methyl - 6 - chloro - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide.	60
35. 3 - Dichloromethyl - 6 - chloro - 7-sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide.	51. 2:3 - Dimethyl - 6 - chloro - 7-sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide.	
15 36. 3 - (1 ¹ :1 ¹ - Dimethyl - 2 ¹ - dimethylaminoethyl) - 6 - chloro - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide.	52. 2 - Ethyl - 6 - chloro - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide.	65
20 37. 3 - Piperidinomethyl - 6 - chloro - 7-sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide.	53. 2 - Methyl - 3 - n - butyl - 6 - chloro - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide.	
25 38. 3 - (3 ¹ - Cyclohexenyl) - 6 - chloro - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide.	54. 2 - Methyl - 3 - n - butyl - 6 - chloro - 7 - (N - methyl - sulphamyl) - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide.	70
39. 3 - Phenoxyethyl - 6 - chloro - 7-sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide.	55. 2 - Methyl - 6 - trifluoromethyl - 7-sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide.	
40. 3 - Acetoxymethyl - 6 - chloro - 7-sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide.	56. 2 - Methyl - 6 - trifluoromethyl - 7 - (N - methyl - sulphamyl) - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide.	75
41. 3 - Acetamidomethyl - 6 - chloro - 7-sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide.	57. 2 - Ethyl - 6 - chloro - 7 - (N - ethyl - sulphamyl) - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide.	80
42. 3 - Diethylaminomethyl - 6 - chloro - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide.	58. 2 - n - Butyl - 6 - chloro - 7 - (N - n - butyl - sulphamyl) - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide.	
43. 3 - Dimethylaminomethyl - 6 - chloro - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide.	59. A physiologically tolerable salt of a compound claimed in any one of Claims 8 to 58.	85
44. 3 - Methylaminomethyl - 6 - chloro - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide.	60. A pharmaceutical preparation which comprises a compound or salt claimed in any one of Claims 1 to 59 in admixture or conjunction with a pharmaceutical carrier suitable for oral or parenteral administration.	90
45. 3 - (2 ¹ - Phenylethyl) - 6 - chloro - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide.	61. Tablets having substantially the composition given in Example 41.	
46. 3 - (1 ¹ - Phenylethyl) - 6 - chloro - 7 - sulphamyl - 3:4 - dihydro - 1:2:4 - benzothiadiazine - 1:1 - dioxide.	ABEL & IMRAY, Quality House, Quality Court, Chancery Lane, London, W.C.2, Agents for the Applicants.	
47. 3 - Ethoxymethyl - 6 - chloro - 7-sulphamyl - 3:4 - dihydro - 1:2:4 - benzo-		

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